Intra-uterine insemination for unexplained subfertility

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Intra-uterine insemination for unexplained subfertility (Review)

Veltman-Verhulst SM, Cohlen BJ, Hughes E, Heineman MJ

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Intra-uterine insemination for unexplained subfertility

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ABSTRACT

Background

Intra-uterine insemination (IUI) is a widely used fertility treatment for couples with unexplained subfertility. Although IUI is less invasive and less expensive than in vitro fertilisation (IVF), the safety of IUI in combination with ovarian hyperstimulation (OH) is debated. The main concern about IUI treatment with OH is the increase in multiple pregnancy rate.

Objectives

To determine whether, for couples with unexplained subfertility, IUI improves the live birth rate compared with timed intercourse (TI), both with and without ovarian hyperstimulation (OH).

Search methods

We searched the Cochrane Menstrual Disorders and Subfertility Group Trials Register (searched July 2011), the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2011, Issue 7), MEDLINE (1966 to July 2011), EMBASE (1980 to July 2011), PsycINFO (1806 to July 2011), SCIssearch and reference lists of articles. Authors of identified studies were contacted for missing or unpublished data.

Selection criteria

Truly randomised controlled trials (RCTs) with at least one of the following comparisons were included: IUI versus TI, both in a natural cycle; IUI versus TI, both in a stimulated cycle; IUI in a natural cycle versus IUI in a stimulated cycle; IUI with OH versus TI in a natural cycle; IUI in a natural cycle versus TI with OH.

Only couples with unexplained subfertility were included.

Data collection and analysis

Quality assessment and data extraction were performed independently by two review authors. Outcomes were extracted and the data were pooled. Subgroup and sensitivity analyses were done where possible.
Main results

One trial compared IUI in a natural cycle with expectant management and showed no evidence of increased live births (334 women: odds ratio (OR) 1.60, 95% confidence interval (CI) 0.92 to 2.8). In the six trials where IUI was compared with TI, both in stimulated cycles, there was evidence of an increased chance of pregnancy after IUI (six RCTs, 517 women: OR 1.68, 95% CI 1.13 to 2.50). A significant increase in live birth rate was found for women where IUI with OH was compared with IUI in a natural cycle (four RCTs, 396 women: OR 2.07, 95% CI 1.22 to 3.50). However the trials provided insufficient data to investigate the impact of IUI with or without OH on several important outcomes including live births, multiple pregnancies, miscarriage and risk of ovarian hyperstimulation. There was no evidence of a difference in pregnancy rate for IUI with OH compared with TI in a natural cycle (two RCTs, total 304 women: data not pooled). The final comparison of IUI in natural cycle to TI with OH showed a marginal, significant increase in live births for IUI (one RCT, 342 women: OR 1.95, 95% CI 1.10 to 3.44).

Authors’ conclusions

There is evidence that IUI with OH increases the live birth rate compared to IUI alone. The likelihood of pregnancy was also increased for treatment with IUI compared to TI in stimulated cycles. One adequately powered multicentre trial showed no evidence of effect of IUI in natural cycles compared with expectant management. There is insufficient data on multiple pregnancies and other adverse events for treatment with OH. Therefore couples should be fully informed about the risks of IUI and OH as well as alternative treatment options.

Plain Language Summary

Intra-uterine insemination for unexplained subfertility

There is evidence that intra-uterine insemination (IUI) improves the odds of becoming pregnant for couples with unexplained subfertility when combined with fertility drugs to induce ovulation.

IUI is a treatment often used for couples with unexplained subfertility. In an IUI cycle, the male partner’s sperm is prepared and placed directly in the uterus at the time of ovulation. IUI cycles can be used in combination with fertility drugs to stimulate the ovaries and increase the number of available eggs. However, these drugs can have adverse effects and also increase the risk of multiple pregnancies. The review of trials found some evidence that IUI increases the chance of pregnancy compared to correct timing of intercourse. There was also evidence of an increased live birth rate in women who underwent IUI and who were also given fertility drugs to stimulate the ovaries. However, increased multiple pregnancy rates are concerning and further studies are needed to assess the magnitude of this problem.

Background

Description of the condition

Of all couples presenting with fertility problems 8% to 28% have no cause that can be identified (NICE 2004). Couples are classified as having unexplained subfertility when they have tried to conceive for at least one year and the fertility work-up showed patent fallopian tubes, an ovulatory menstrual cycle and a normal semen analysis.

Description of the intervention

Intra-uterine insemination (IUI) is a commonly used treatment in couples with unexplained subfertility. IUI is a relatively simple procedure in which semen is ‘washed’ in the laboratory and inserted in the uterine cavity using a small catheter at the time of ovulation. IUI can be performed with or without drugs for ovarian hyperstimulation (OH). For correct timing of the insemination, cycle monitoring is performed. This is usually done by ultrasound assessment of follicle growth or by monitoring the preovulatory luteinizing hormone rise in blood or urine. In hyperstimulated cycles ovulation is often induced by an injection of human chorionic gonadotropin (hCG), which improves timing possibilities. In con-
trast to the IUI procedure, with expectant management couples receive cycle monitoring for correct timing of sexual intercourse, for example timed intercourse (TI), or no intervention at all.

How the intervention might work

The rationale for performing IUI is that the motile spermatozoa, which are morphologically normal, can be concentrated in a small volume and placed directly into the uterus close to the released oocyte. In this way the cervix, which also acts as a reservoir for sperm, is bypassed. Accurate timing of the insemination is therefore of great importance. IUI can be performed with or without ovarian hyperstimulation (OH). The two most commonly used drugs for ovarian hyperstimulation are clomiphene citrate (CC), which is an oral treatment, and gonadotropins administered by subcutaneous injection. The aim of OH is to increase the number of oocytes available for fertilisation and to enhance accurate timing.

The role of IUI in fertility treatment is often debated, in particular in terms of whether or not it is superior to TI and whether or not OH should be used at the same time (Cohlen 2005; Hughes 2003; Stewart 2003).

Why it is important to do this review

The first randomised controlled trial (RCT) of IUI for male factor infertility was published in 1984 and reported a favourable outcome for IUI compared with TI (Kerin 1984). Since then many trials have studied the efficacy of IUI for unexplained subfertility, with variable results. Subsequent RCTs have compared IUI with TI, with or without OH, and suggested a benefit of OH in combination with IUI (Hughes 1997). Goverde and colleagues reported that mild ovarian hyperstimulation of IUI cycles did not yield higher pregnancy rates (Goverde 2000), though IUI is more cost-effective compared with in vitro fertilisation (IVF). Others stated that IUI alone is not efficacious, without some form of ovarian hyperstimulation (Bhattacharya 2008; Guizick 1998). Some studies suggested that both OH and IUI independently contributed to increased pregnancy rates (Aboulghar 2003; Hughes 1997). A meta-analysis of seven studies showed a significantly higher pregnancy rate for treatment with gonadotropins (28%) compared to treatment with CC (19%) when combined with IUI (Cantineau 2009).

Although ovarian hyperstimulation seems to result in higher pregnancy rates it also increases the incidence of multiple pregnancies and ovarian hyperstimulation syndrome (OHSS). These pose serious risks to the health of both mother and baby (Fauser 2005; Gleicher 2000; Nan 1994). The NICE fertility guidelines recommended IUI without OH for couples with unexplained subfertility because of the increased risk of multiple pregnancies and OHSS associated with OH (NICE 2004). This systematic review was therefore undertaken to assess the evidence on the benefits and side effects of IUI with or without OH, compared to timed intercourse, for couples with unexplained subfertility.

OBJECTIVES

To determine whether for couples with unexplained subfertility IUI improves the live birth rate compared with timed intercourse (TI) or expectant management, both with and without ovarian hyperstimulation (OH).

METHODS

Criteria for considering studies for this review

Types of studies

Only truly randomised controlled trials were included. Quasi-randomised studies where allocation, using for example alternation or chart number, was subject to manipulation were excluded. Attempts were made to contact the author of the study if the randomisation or allocation method was unclear. Trials that did not report separate data for women with unexplained subfertility and where such data were not obtainable from the authors were excluded. The trial design was assessed (crossover or parallel). Crossover trials were included if pre-crossover data could be extracted.

Types of participants

1. Couples with unexplained subfertility defined as follows. Normal ovulatory status (determined by either biphasic basal body temperature chart, normal luteal progesterone, in phase endometrial biopsy or ovulation detected with ultrasound). Tubal patency (determined by hysterosalpingography or laparoscopy, or both). A normal semen sample according to World Health Organization (WHO) criteria current at the time of trial. Sperm concentration of at least 20 x 10^6 per ml:
- total motility of at least 50%,
- normal morphology of at least 30% (WHO 1987, at least 50%) or Kruger criteria,
- no anti-sperm antibodies.
2. Couples who had tried to conceive for at least one year. Participants excluded were:
- couples with a known cause of infertility including a moderate male factor, moderate to severe endometriosis (according to the
American Society for Reproductive Medicine (ASRM) classification), tubal disease and a cervical factor. Authors were contacted to obtain data of couples with unexplained infertility if groups of mixed infertility causes were studied. If relevant data could not be extracted separately for included participants the study was excluded. Trials that included patients with mild to moderate endometriosis only were excluded.

**Types of interventions**

Trials with at least one of the following comparisons:
- intra-uterine insemination (IUI) versus timed intercourse (TI), both in a natural cycle;
- IUI versus TI, both in a stimulated cycle;
- IUI in a natural cycle versus IUI in a stimulated cycle;
- IUI in a stimulated cycle versus TI in a natural cycle;
- IUI in a natural cycle versus TI in a stimulated cycle.

Ovarian hyperstimulation (OH) was achieved with either clomiphene citrate or gonadotropins. Expectant management was included as a variant of timed intercourse.

Interventions excluded:
- intra-cervical insemination, because we consider this to be a different treatment modality (Ripps 1994) and it is the topic of another review (Besselink 2008);
- donor insemination.

**Types of outcome measures**

**Primary outcomes**
Live birth rate per couple (all cycles)

**Secondary outcomes**
- Live birth per couple after one treatment cycle
- Pregnancy rate per couple (all cycles)
- Pregnancy rate per couple after one treatment cycle

Adverse events:
- moderate or severe ovarian hyperstimulation syndrome (OHSS), rate per woman;
- multiple pregnancy rate per couple;
- miscarriage rate per couple;
- ectopic pregnancy rate per couple.

Clinical pregnancy was defined by the presence of an intra-uterine gestational sac or fetal heartbeat visualised by an ultrasound scan. Biochemically confirmed only pregnancies were excluded. When pregnancy was not further defined, and remained unclear even after contacting the authors, the pregnancy was assumed to be clinical. Ongoing pregnancy was defined as a pregnancy extending beyond 12 weeks of gestation, confirmed by ultrasound or delivery.

Data on moderate or severe OHSS were collected. Multiple pregnancies confirmed by ultrasound, with or without selective reduction, were recorded. An intention-to-treat (ITT) analysis was used whenever possible. Women who dropped out or were excluded after randomisation were assumed not to be pregnant. Women who were excluded because they conceived before receiving treatment were included as a success in the allocated group in the ITT analysis.

**Search methods for identification of studies**

We have searched for all reports which describe (or might describe) randomised controlled trials of IUI with or without OH. The original search was performed in 2005 and the search was updated in 2010. We have used the search strategy developed by the Cochrane Menstrual Disorders and Subfertility Group (see Review Group details in the Cochrane Library for more information).

**Electronic searches**

We searched the:
- Cochrane Menstrual Disorders and Subfertility Group Specialised Register (searched July 2011),
- Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2011, Issue 7),
- MEDLINE (1966 to July 2011) (Appendix 1),
- EMBASE (1980 to July 2011) (Appendix 2),
- PsycINFO (1806 to July 2011),
- SCIssearch, and
- reference lists of articles.

**Searching other resources**

The citation lists of relevant publications and included studies were searched. We handsearched abstracts of the American Society for Reproductive Medicine (ASRM) and European Society for Human Reproduction and Embryology (ESHRE). Authors were contacted to obtain additional information, where necessary.

**Data collection and analysis**

**Selection of studies**

Two review authors (SMV, BJC) independently selected the trials to be included according to the above-mentioned criteria. Disagreements were resolved by discussion.
Data extraction and management
Data extraction was done independently by two authors (SMV, EH). Disagreements were resolved by discussion. A statistician (AV) was consulted for data extraction and calculation of data from crossover trials, when possible.

Assessment of risk of bias in included studies
The included trials were screened by a predesigned inclusion form (by SMV, BJC) for the following quality criteria and methodological details.

Trial characteristics
1. Method of randomisation and sequence generation
2. Quality of allocation concealment (assessed according to the Cochrane standards; studies with an adequate allocation score or where the allocation concealment was unclear were included in the meta-analysis)
3. Crossover or parallel design
4. Number of couples randomised, excluded or lost to follow up
5. Details on dropouts
6. Whether an intention-to-treat (ITT) analysis was done or could be extracted
7. Percentage of cancelled cycles
8. A power calculation performed beforehand
9. Duration, timing and location of the study

These details were summarised and entered in the 'Risk of bias' table for each included study and presented in Figure 1 and Figure 2.

Figure 1. Methodological quality graph: review authors’ judgements about each methodological quality item presented as percentages across all included studies.
Figure 2. Methodological quality summary: review authors’ judgements about each methodological quality item for each included study.
Measures of treatment effect
Statistical analysis of results followed the guidelines of the Cochrane Menstrual Disorders and Subfertility group (Cochrane Handbook 2011). Dichotomous data for each study were summarised in a two-by-two table and expressed as an odds ratio (OR) with 95% confidence interval (CI).

Unit of analysis issues
Data were analysed per randomised couple, because per treatment cycle data lead to biased results (Dias 2008). In the case of a crossover trial, only data prior to crossover were analysed.

Dealing with missing data
Authors of the published trials were contacted in the case of missing data. The newly obtained data were included in the analysis. Analyses were done according to the ITT principle when possible.

Assessment of heterogeneity
Heterogeneity between the results of different studies was examined by inspecting the scatter in the data points on the graphs and the overlap in their confidence intervals, and by checking the $I^2$ statistic.

Assessment of reporting biases
To detect publication bias a funnel graph, plotting sample size versus effect size, was performed where possible.

Data synthesis
Where appropriate, the data were pooled and a meta-analysis was performed with RevMan software (using the Peto-modified Mantel-Haenszel method) using both a fixed-effect model and random-effects model. Published graphs display the results of the fixed-effect approach. When pre-crossover data were available, crossover trials were included in the analysis and pooled with parallel trials. Stratification for number of treatment cycles was done by analysing the first cycle, one to three cycles and more than three cycles separately, where possible.

Subgroup analysis and investigation of heterogeneity
A subgroup analysis regarding methods of ovarian hyperstimulation was performed. Heterogeneity was assessed by the $I^2$ statistic. An $I^2$ value of greater than 50% was considered as substantial heterogeneity. In the case of statistical heterogeneity the original trials were studied for clinical heterogeneity.

Sensitivity analysis
Specific items that we explored were as follows:
1. trials with adequate methodology versus those of poor methodology, where adequate methodology was defined as an adequate randomisation method, adequate allocation concealment, analysis by intention to treat and losses to follow up of less than 20%;
2. trials which might differ from others with respect to their participants, interventions or clinical criteria for defining outcomes.

RESULTS
Description of studies
See: Characteristics of included studies; Characteristics of excluded studies.

Results of the search
Over 700 articles were found in the initial search of databases. Of these, 198 were related to the subject. Their abstracts were searched by hand. This resulted in the selection of 25 trials reporting one or more of the comparisons of interest. A search performed in August 2010 retrieved two additional RCTs with a comparison of interest. The search was updated in July 2011 and one further article was retrieved (Wordsworth 2011) which relates to one of the included studies (Bhattacharya 2008): this article awaits assessment. Attempts were made to contact all authors to retrieve unpublished details. Fifteen replies were received. Three replies resulted in the exclusion of the trial (Nulsen 1993; Prentice 1995; Serhal 1988). Five authors (Agarwal 2004; Arici 1994; Bhattacharya 2008; Guzick 1999; Melis 1995; Murdoch 1991; Steures 2006) provided unpublished information or data, which were used in this analysis. Some authors could not provide us with the requested data. Others never returned the form.
Included studies

A total of 14 RCTs were included. All trials were published in journals (Janko 1998 was published as an abstract only) and were available in English.

Further details about the included trials are provided in the 'Characteristics of included studies' table and in the additional 'Quality features' table (Table 1) and 'Prognostic factors' table (Table 2).

Number of trials included per comparison

1. IUI versus TI both in a natural cycle: one (Bhattacharya 2008). Two other studies with this comparison were identified (Kirby 1991; Martinez 1990). These studies were excluded from the analysis because they reported post-crossover per cycle data only.


4. IUI in a stimulated cycle versus TI in a natural cycle: two (Deaton 1990; Steures 2006).

5. IUI in a natural cycle versus TI in a stimulated cycle: one (Bhattacharya 2008).

Martinez 1990 studied all five comparisons, however there were no pre-crossover data available for couples with unexplained subfertility. Agarwal 2004, although included in the review, was excluded from the primary analysis. This Indian study had a high dropout percentage (37%) in the treatment group which caused severely unbalanced groups. Because the main reason for dropout was due to financial constraints this introduces a considerable bias. However, a sensitivity analysis including this study was performed, see Table 3.

In the most recent included studies, from Bhattacharya 2008 and Steures 2006, expectant management was performed instead of TI.

The trials were carried out in different countries: USA (Arici 1994; Deaton 1990; Guzick 1999), Italy (Arcaini 1996; Melis 1995), UK (Bhattacharya 2008; Chung 1995; Murdoch 1991), India (Agarwal 2004), the Netherlands (Goverde 2000; Steures 2006), Slovakia (Janko 1998), Sweden (Karlstrom 1993), and different countries in Europe (ESHRE - Crosignani 1991).

Types of subfertility

The definition of unexplained subfertility was similar between studies. Six trials enrolled participants with unexplained subfertility only. Six trials also included participants with male factor subfertility. In these studies the data for unexplained subfertility were either reported separately or obtained from the author. One study selected couples with unexplained subfertility and an intermediate prognosis (Steures 2006). Three studies (Arici 1994; Deaton 1990; Karlstrom 1993) reported the inclusion of women with surgically corrected minimal or mild endometriosis, which we considered to be unexplained subfertility. Melis 1995 specifically excluded patients if minor disorders such as minimal endometriosis were found in the investigation. Although our protocol stated to only include women with minimal and mild endometriosis we decided to include Deaton 1990 despite the inclusion of three patients (out of 51 patients in total) with moderate endometriosis. All studies reported a thorough fertility investigation, including a laparoscopy. A semen analysis was performed at least once in all studies. In nine studies the semen quality was reported according to the WHO criteria. Three studies (Arcaini 1996; Janko 1998; Steures 2006) did not specify the criteria for a normal semen analysis. Chung 1995 used a sperm count per ejaculate instead of per ml. The data of Guzick 1999 were based only on a normal sperm count and a normal motility according to Kruger criteria.

Primary or secondary subfertility

Nine trials contained a mixed population of couples who had never achieved a pregnancy (primary subfertility) and those who had previously been pregnant (secondary subfertility). The remaining trials did not give any description for inclusion of people with secondary subfertility.

Previous treatment

Couples who have previously failed fertility treatment have a lower probability of conception in subsequent treatment attempts. It is, therefore, important in fertility trials to report if couples have undergone previous treatment. Of the 14 included studies only one trial included couples who had previously failed fertility treatment.
Interventions

The treatment methods varied substantially between studies. Seven studies used gonadotropins for ovarian hyperstimulation. Arcaini 1996 offered both gonadotropins and clomiphene citrate, which resulted in a high dose hyperstimulation. Five studies used clomiphene only, and Crosignani 1991 did not report the method of ovarian hyperstimulation. The different fertility centres in this multicentre trial used different treatments. More details on drug dose and method can be found in the prognostic factor table (Table 2) and ‘Characteristics of included studies’ table. Additional gonadotropin releasing hormone agonist (GnRHa) was used by Chung 1995 and Murdoch 1991. All studies used human chorionic gonadotropin (hCG) (5000 to 10,000 IU) for triggering ovulation. Chung also provided hCG in the post-ovulatory phase. The timing of IUI was similar among the studies. Follicle development was usually monitored by ultrasound scan (USS) and serum estradiol levels (serum-E2). The hCG was given when the dominant follicles reached a mean diameter of 16 to 18 mm. Insemination was performed 30 to 48 hours after hCG administration. Arcaini 1996 performed a double insemination at 24 and 48 hours, and in the trial by Murdoch 1991 insemination took place on alternate days until ovulation was confirmed. Follicular development in natural cycles was monitored by ultrasound or luteinizing hormone urine tests, and intercourse was advised at 12 to 40 hours after the hCG or LH surge. Couples were mostly advised to have intercourse more than once.

In the studies with expectant management instead of TI (Bhattacharya 2008; Steures 2006), couples were given general advice regarding the need for regular intercourse.

Cancellation criteria

The most serious adverse effects of ovarian hyperstimulation are multiple pregnancies and OHSS. These risks can both be reduced by the cancellation of the treatment cycle if excessive follicle stimulation occurs. It is important that fertility trials report the cancellation criteria they applied. Firstly, to ensure that patients were not exposed to a higher risk of multiple pregnancy or OHSS to increase the pregnancy rate and secondly, to reduce the bias introduced by cancellation of treatment in initially randomised groups. Ten studies described criteria for cancellation of the treatment cycle. Insemination or hCG administration did not take place if the cancellation criteria were met. Five studies used serum-E2 levels to determine over- or under-stimulation as well as a maximum of dominant follicles (four follicles of a maximum 16 mm diameter).

Arcaini 1996 accepted a maximum of six dominant follicles. Four studies did not describe any cancellation criteria.

Outcomes

Nine trials reported live birth, our primary outcome of interest. The other studies reported pregnancy as the main outcome. Pregnancy was confirmed by ultrasound in nine trials. In Guzick 1999 pregnancy was confirmed by two hCG measurements or live birth. Others did not report the method of pregnancy confirmation. The reported pregnancies were mostly clinical. The multiple pregnancy rate was mentioned in 12 trials, miscarriage in 10, ectopic pregnancy in 10, and OHSS in nine trials. These events were often reported as total numbers or as post-crossover data and therefore often could not be used in the meta-analysis.

Power calculation

Bhattacharya 2008, Goverde 2000 and Steures 2006 were the only studies in which a power calculation was performed. All three studies reached the targeted inclusion number to obtain enough power (80% to 90% with 5% level of significance) to detect a clinical relevant improvement in live birth rate or pregnancy rate.

Intention to treat

An intention-to-treat (ITT) analysis was used when possible. In three trials an ITT analysis was not possible (Crosignani 1991; Deaton 1990; Karlstrom 1993) as the trials only reported the number of patients analysed. In Murdoch 1991 one woman became pregnant spontaneously between treatment cycles. This pregnancy resulted in a live birth and was entered as such in the analysis. Goverde 2000 also reported spontaneous pregnancies that occurred between treatment cycles. Because it was unclear in which group these pregnancies occurred, they could not be used in the ITT analysis.

Excluded studies

Thirteen studies were excluded (see ‘Characteristics of excluded studies’ table). Six studies clearly did not meet the inclusion criteria. Two studies were found not to be randomised studies (Aboulghar 1993; Serhal 1988). An inadequate method of randomisation was the reason for exclusion of another two trials (Nulsen 1993; Prentice 1995). One study (Tummon 1997) included women with endometriosis only and thus did not focus on unexplained subfertility. Martinez et al (Martinez 1990) reported biochemically confirmed pregnancies only and was therefore excluded.
Another seven studies were excluded because the appropriate data needed for the meta-analysis were not obtainable. Ho 1998 did not report separate data for the couples with unexplained subfertility. Six studies (Doyle 1991; Evans 1991; Gregoriou 1995; Kirby 1991; Martinez 1991; Zikopoulos 1993) reported post-crossover per cycle data only, instead of per randomised woman, and therefore could not be included. We contacted all authors to obtain pre-crossover data.

Studies awaiting assessment
There are no studies awaiting assessment. However if pre-crossover data of the excluded studies become available we will reconsider inclusion and process the studies in an update of this review.

Risk of bias in included studies
The overall risk of bias was substantial (see Table 1, Figure 1, Figure 2). This was largely due to the lack of information on allocation concealment and randomisation in many of the trials.

Allocation
The randomisation or allocation concealment method was generally poorly described. Bhattacharya 2008, Chung 1995, Goverde 2000 and Steures 2006 were the only truly randomised trials that described the methods of randomisation and allocation concealment in their publication. Five authors provided the randomisation or allocation details after correspondence (Agarwal 2004; Arici 1994; Guzick 1999; Melis 1995; Murdoch 1991). The remaining five trials did not report the methods used.

Blinding
None of the studies reported blinding. In trials comparing IUI with TI blinding is not possible. Trials comparing IUI with or without OH could be blinded. However, the use of subcutaneously administered ovarian hyperstimulation drugs complicates this.

Incomplete outcome data
Seven of the 14 included trials clearly mentioned the number of and the reasons for dropping out (Arici 1994; Deaton 1990; Goverde 2000; Guzick 1999; Melis 1995; Murdoch 1991; Steures 2006). Bhattacharya 2008 had a loss to follow-up of less than 1%. The studies with the highest losses to follow-up were Arcaini 1996 (dropout of 20.6%) and Agarwal 2004 (19%). In Agarwal the couples mainly left the study for financial reasons, which resulted in an unevenly distributed dropout rate of 37% in the treatment group as compared to 1% in the control group. The dropout rate usually increased in studies with a longer follow-up period. Because this review included trials with different durations, it was difficult to compare the dropout rates.

Selective reporting
There is a risk of selective reporting in this review. Live birth data were not reported in five studies (Arcaini 1996; Crosignani 1991; Deaton 1990; Janko 1998; Karlstrom 1993). Adverse events were often not reported per group but as study total, which could not be included in the analysis. Multiple pregnancy rates were not reported in two trials (Crosignani 1991; Janko 1998).

Other potential sources of bias
To reduce bias introduced by a crossover study design, we included pre-crossover data only. This resulted in a selection of the eligible studies. Three studies used a crossover design (Arici 1994; Crosignani 1991; Deaton 1990). In this design patients were initially randomised to the treatment or control group but then crossed-over to the other group after a certain number of treatment cycles. The duration of these studies varied from two to eight treatment cycles per couple. In two studies (Arici 1994; Crosignani 1991) the patients crossed over after one treatment cycle. In Deaton 1990 patients crossed over after four cycles. Nine studies used a parallel design, in which patients stayed in the group to which they were randomised. These trials offered a total of one to six treatment cycles per couple.

Effects of interventions
This section describes the results of the meta-analyses and sensitivity analyses. The results of the two main comparisons are also presented in additional Table 3 and Table 4.

Comparison 1. IUI versus TI or expectant management both in a natural cycle
The results from this comparison are all obtained from the study of Bhattacharya 2008. Data for the unexplained subfertility group only were provided by the author.

Live birth rate per couple
Analysis 1.1
Analysis comprised a total of 334 couples with unexplained subfertility only. A live birth rate of 23% was obtained in the IUI group versus 16% in the expectant management group. The live birth rates were not significantly different (OR 1.60, 95% CI 0.92 to 2.78).
Pregnancy rate per couple

Analysis 1.2

There was no evidence of a significant difference in pregnancy rates (OR 1.53, 95% CI 0.88 to 2.64). Of the 167 patients treated with IUI, 38 became pregnant compared to 27 of the 167 untreated patients.

Adverse events

Multiple pregnancy (Analysis 1.3)

Three multiple pregnancies were reported in the unexplained subfertility group, two of which occurred in the expectant management group. The multiple pregnancy rate per ongoing pregnancy was 7% for expectant management and 3% for IUI treated patients. This resulted in no significant difference between the IUI and TI groups (OR 0.50, 95% CI 0.04 to 5.53).

Miscarriage (Analysis 1.4)

Sixteen miscarriages were reported, seven in the IUI group and nine in the TI group (OR 0.77, 95% CI 0.28 to 2.11).

Ectopic pregnancies (Analysis 1.5)

Two ectopic pregnancies occurred in the IUI group (OR 5.06, 95% CI 0.24 to 106.21).

Comparison 2. IUI versus TI both in stimulated cycles

Live birth rate per couple

Analysis 2.1

Only two of the six trials included in the analysis reported live birth rates (n = 208). There was no significant difference between the probability of a live birth in women who underwent IUI compared with the TI group (OR 1.59, 95% CI 0.88 to 2.88). Statistical heterogeneity was detected (P = 0.06, I² = 71.7%) between the two studies. This may be explained by the fact that all patients in the Melis study had previously received fertility treatment.

Pregnancy rate per couple

Analysis 2.2

All six trials reported pregnancy rates per couple. There were 517 women included in this analysis and 149 pregnancies were reported. The OR showed a statistically significant higher pregnancy rate in the IUI group (OR 1.68, 95% CI 1.13 to 2.50) if all cycles were analysed. To check sensitivity to the model assumptions, the random-effects model was used and showed a similar result (OR 1.71, 95% CI 1.11 to 2.63). There was no statistical heterogeneity (P = 0.40, I² = 4.7%).

If the study by Agarwal 2004 was included in the analysis the results change markedly. The OR become 1.09 (95% CI 0.77 to 1.54), crossing the line of no evidence of effect. Including this study also introduced a strong heterogeneity (P = 0.001, I² = 65.4%). This statistical heterogeneity caused by Agarwal 2004 supports our concerns about the validity of this trial, both from a statistical (high probability of bias) and from a clinical point of view. On the other hand, this sensitivity analysis showed the relative weakness of the significant difference we found. Therefore, our results should be interpreted with caution.

A subgroup analysis for the number of treatment cycles was performed. If we analysed the first treatment cycle only, no significant difference in pregnancy rate was seen (OR 1.48, 95% CI 0.71 to 3.11) and no heterogeneity detected (I² = 0%). As expected, cumulative pregnancy rates increased with a rising number of treatment cycles per couple. We were unable to determine the optimal number of treatment cycles that a couple should be offered.

Adverse events

Because only few studies mentioned adverse events (multiple pregnancies, miscarriage, ectopic pregnancies or OHSS) per treatment arm, no conclusions could be drawn regarding the effect of IUI compared with TI on these events.

Multiple pregnancy (Analysis 2.4)

The trials reported a total of 21 multiple pregnancies. Arcaini 1996, Chung 1995 and Karlstrom 1993 reported one high order multiple pregnancy each. Only four studies reported their multiple pregnancies per treatment arm, 11 in the IUI group and six in the TI group (representing 13.5% of the total number of pregnancies in these studies). Pooling these studies resulted in no significant difference (OR 1.46, 95% CI 0.55 to 3.87) and no heterogeneity (I² = 0%).

Miscarriage (Analysis 2.5)

Twenty-seven miscarriages were reported in total. Fifteen were reported per treatment arm, nine in the IUI group and six in the TI group (OR 1.66, 95% CI 0.56 to 4.88). No heterogeneity was found (I² = 0%).

Ectopic pregnancy (Analysis 2.6)

There were not enough data available to analyse the ectopic pregnancy rate. The occurrence of an ectopic pregnancy was reported in two studies only.

Ovarian hyperstimulation syndrome (Analysis 2.3)

With only one event of OHSS reported it appeared that OHSS rarely occurs in treatment programs of IUI in stimulated cycles.

Comparison 3. IUI in a natural cycle versus IUI in a stimulated cycle

Our main outcome, live birth, was reported in all included studies. For comparison reasons pregnancy rates were also calculated, if pregnancy data were not published the live birth data were used.
Live birth rate per couple
Analysis 3.1
Three trials reported the number of live births per treatment arm (Arici 1994; Goverde 2000; Murdoch 1991). The live birth data of Guzick 1999 were obtained after correspondence. A significant increase in live births was found for women treated with IUI and OH compared to women treated with IUI only (OR 2.07, 95% CI 1.22 to 3.50). The random-effects model and analysis without ITT had similar results. No statistical heterogeneity was detected ($I^2 = 0\%$).

Pregnancy rate per couple
Analysis 3.2
The pregnancy rates of Arici 1994 and Murdoch 1991 were pooled with the live birth data of Goverde 2000 and Guzick 1999 in this analysis, as Goverde and Guzick did not publish clinical pregnancy rate data. The outcome of this analysis should be interpreted as an underestimation of the real pregnancy rate because miscarriages are not included in this calculation. The OR for clinical pregnancy per woman randomised was 2.14 (95% CI 1.26 to 3.61), which was significantly in favour of IUI combined with OH. No heterogeneity was found.

Adverse events
Multiple pregnancy (Analysis 3.4)
Goverde 2000 reported an overall multiple pregnancy rate of 29% in the OH group (with both male and unexplained subfertility). Guzick 1999 reported an overall multiple pregnancy rate of 13% in the OH group. This also included patients with male subfertility and patients undergoing intra-cervical insemination. No multiple pregnancies occurred during the trial of Arici 1994, and Murdoch 1991 reported one twin pregnancy only in the OH group. A meta-analysis could not be performed.

Miscarriage (Analysis 3.5)
One miscarriage in the OH group was reported by Arici 1994. Guzick 1999 reported a total miscarriage rate of approximately 24% in all couples undergoing IUI treatment.

Ectopic pregnancy (Analysis 3.6)
Guzick 1999 reported three ectopic pregnancies in the group treated with IUI and OH.

OHSS (Analysis 3.3)
Six of the 932 women treated in Guzick 1999 required hospitalisation for OHSS. In the other three trials no women developed moderate or severe OHSS.

Comparison 4. IUI in a stimulated cycle versus TI or expectant management in a natural cycle

The results of this comparison were collected from Deaton 1990 and Steures 2006. Because Steures 2006 selected couples with an intermediate chance of spontaneous pregnancy only, pooling of both studies was not considered adequate.

Live birth rate per couple
Analysis 4.1
This was only reported by Steures 2006 and showed no significant difference in live birth rate (OR 0.82, 95% CI 0.45 to 1.49); 20% of the IUI combined with OH treatments resulted in a live birth while 24% of the patients in the expectant management group had a live born child.

Pregnancy rate per couple
Analysis 4.2
There was no evidence of a significant difference in pregnancy rates for both Deaton 1990 (OR 4.05, 95% CI 0.39 to 41.87) as for Steures 2006 (OR 0.61, 95% CI 0.25 to 1.47).

Adverse events
Analysis 4.4
No multiple pregnancies occurred in Deaton 1990 and there were three in Steures 2006, two of which occurred in the IUI with OH group (OR 2.00, 95% CI 0.18 to 22.34). No women developed OHSS. Miscarriage rates were not significantly different between the groups (Analysis 4.5). Ectopic pregnancies were not reported.

Comparison 5. IUI in a natural cycle versus TI in a stimulated cycle

Bhattacharya 2008 studied this comparison with IUI in a natural cycle compared to TI in a clomiphene citrate stimulated cycle.

Live birth rate per couple
Analysis 5.1
Live birth rates were 23% and 13% for women treated with IUI compared to TI in a stimulated cycle, respectively. There was a small but significant difference in favour of IUI in a natural cycle (OR 1.95, 95% CI 1.10 to 3.44) for couples with unexplained subfertility.
**Pregnancy rate per couple**

Analysis 5.2

A marginal significant effect was found in the ongoing pregnancy rate (OR 1.77, 95% CI 1.01 to 3.08).

**Adverse events**

Multiple pregnancy (Analysis 5.3)

There were two multiple pregnancies, one in each group.

Miscarriage (Analysis 5.4)

The miscarriage rate was evenly distributed among groups (OR 0.91, 95% CI 0.32 to 2.58).

Ectopic pregnancies (Analysis 5.5)

Two ectopic pregnancies occurred in the IUI group resulting in a non-significant difference with a wide CI (OR 5.30, 95% CI 0.25 to 111.26).

**DISCUSSION**

**Summary of main results**

The aim of this review was to analyse the effectiveness of intra-uterine insemination (IUI), with or without ovarian hyperstimulation (OH), by systematically evaluating the best available evidence. Because randomised controlled trials (RCTs) are still considered to provide the best assessment of the effectiveness of treatments (Hughes 2003; Johnson 2003), we included only truly randomised trials in this review. The individual trials were contradictory and often lacked sufficient power to draw firm conclusions. In spite of these shortcomings, and also some clinical heterogeneity, we were able to pool their results and draw some conclusions.

This meta-analysis of 14 RCTs showed a significant increase in pregnancy rates for treatment with both intrauterine insemination (IUI) and ovarian hyperstimulation (OH). We can therefore conclude that in couples with unexplained subfertility the combination of OH and IUI seems to be the most effective treatment modality.

The comparison of IUI versus TI, both in stimulated cycles, showed an odds ratio for pregnancy rate per couple of 1.68 (95% CI 1.13 to 2.50) in favour of IUI. It seems appropriate, therefore, to combine IUI and OH. However, the following points need to be taken into account. Firstly, there was insufficient evidence to conclude that IUI in combination with OH improved live birth rates when compared with TI in stimulated cycles. This might be the result of insufficient power, a total of 208 couples in two trials only were included (Chung 1995; Melis 1995), or the fact that Melis included a population with a poor prognosis (all patients had previously failed treatment with IUI and OH). Because this study makes up half of the live birth analysis it could mask the promising results from Chung 1995.

Secondly, the results varied according to whether or not one study (Agarwal 2004) was included. In the meta-analysis six studies were included, in which a total of 517 women were randomised to either treatment with OH alone or with IUI and OH. The inclusion of Agarwal 2004 (n = 140), which had been excluded due to a high risk of bias caused by losses to follow-up, in a sensitivity analysis resulted in no evidence of effect. The sensitivity of our results after inclusion of a relatively small study emphasises the fragility of our analysis. However, the trial by Agarwal 2004 showed an unexpected high pregnancy rate in the control group compared to the treatment group (29% higher). Because there is no reason to believe that timed intercourse would increase the pregnancy rate compared to IUI, and because of the high dropout rate, this study should not be considered representative. It would be more realistic to assume that there is no difference between IUI and TI. Our calculations indicate that it would take a trial of approximately 400 participants showing no difference between IUI and TI to reduce the lower confidence limit to one.

Thirdly, the pooled studies were clinically heterogeneous. There was, however, no evidence of statistically significant heterogeneity. This suggests that the different factors had little effect on the overall conclusions; the included studies differed markedly in terms of treatment methods and quality. The pooled studies also used different treatment protocols. The type of OH drug and dose, the treatment duration and cancellation criteria could have influenced the outcomes. For example, the highest pregnancy rate per couple was found in the study by Arcaini 1996. A reason for this could be that this study used the most aggressive stimulation method, accepted a maximum of six dominant follicles and treated couples for up to five cycles. There were also variations in the patient population among the included studies that could have influenced the outcome, such as previous treatment and the inclusion of women with endometriosis. On the other hand, our results were not sensitive to the inclusion or exclusion of trials on the basis of the above-mentioned parameters.

Fourthly, the clinical relevance of the result is questionable. The analysis shows evidence of a significant increase in pregnancy rate for cumulative cycles only. What does it clinically mean if the odds to become pregnant for a woman undergoing IUI treatment is 1.68 times higher than for a woman treated with OH alone if the treatment duration could vary from one to up to five cycles? Stratification for treatment duration gave no evidence of an increase in pregnancy rate if only first cycle data were analysed. This implies that it takes more than one treatment cycle to significantly improve the couple’s chances. However, it was not possible to give any clarity about the optimal number of treatment cycles in this review. A risk difference was calculated for the analysis of one to three treatment cycles, to extract the numbers needed to treat. Based on these results, approximately 13 couples need to be treated with one to three cycles of IUI and OH to result in one.
additional pregnancy. Furthermore, the clinical relevance of the results is also dependent on the baseline fecundity of a couple. Unfortunately there were not enough data available in this meta-analysis to perform subgroup analyses for prognostic factors, such as age and duration of subfertility. Overall, we can conclude that an odds ratio of 1.68 for treatment over one to five cycles for couples with different prognoses and baseline fecundity is not specific enough to be helpful in a clinical setting.

Finally, the impact of IUI on multiple pregnancies, ovarian hyperstimulation syndrome, miscarriage and ectopic pregnancy could not be estimated due to a lack of information. Adverse events were often not mentioned, or mentioned per group instead of per treatment modality. The studies mentioning 'no events' were included in the meta-analyses, which might result in underestimation of the adverse events. On the other hand, these adverse events are mostly accredited to OH and not to IUI. It seems therefore unlikely that any significant difference in adverse events would be found when OH with TI is compared to OH with IUI.

The comparison IUI in a natural cycle with IUI in a hyperstimulated cycle revealed a more than two-fold increase in live birth rate in women treated with OH (OR 2.07, 95% CI 1.22 to 3.50). This result could be considered robust. The analysis comprised 396 couples and included high quality trials. A study with 1500 couples showing no treatment effect is needed to reduce the lower confidence limit to one. If we use these data to calculate the numbers needed to treat, with an assumed control risk of 14%, we would find that approximately nine couples need to be treated with IUI and OH for approximately four cycles to result in one additional live birth compared to the control group. These data should be interpreted with caution because the impact of OH on multiple pregnancies and other adverse effects could not be answered by this review.

The use of OH in fertility treatment for unexplained subfertility has been both supported and criticised. When Hughes published a meta-analysis indicating that the average fecund ability is approximately five-fold higher for treatment with IUI and OH (Hughes 1997), the Royal College of Obstetricians and Gynaecologists (RCOG 1998) concluded accordingly that “OH with IUI is an effective treatment for couples with unexplained infertility”. However, major concerns about the incidence of multiple pregnancies were raised and OH became less popular. These concerns have resulted in an adjustment of the advice for treatment of couples with unexplained subfertility. The NICE fertility guideline states that “ovarian hyperstimulation should not be offered, even though it is associated with higher pregnancy rates, because it carries a risk of multiple pregnancy” (NICE 2004). The absence of a known reason for not getting pregnant in unexplained subfertility makes it difficult to target treatment. The rationale for treatment with OH is to increase the number of mature follicles and trigger ovulation to facilitate optimum timing of IUI. It may also correct subtle abnormalities in follicular maturation and fertilisation and may improve the endometrial quality (Guzick 1998).

The increase of multiple pregnancies is a logical consequence of stimulated growth of multiple follicles. The incidence of multiple pregnancies after treatment with OH and IUI varies between 10% and 40%, and the overall contribution of this treatment to multiple births is estimated to be around 30% (Fauser 2005). The question is whether this multiple pregnancy rate is acceptable or whether it can be reduced to acceptable numbers. Recently, more and more evidence is being collected that mild ovarian hyperstimulation with strict cancellation criteria minimizes the risk of achieving multiple pregnancies to approximately 10%, without compromising pregnancy rates (ESHRE 2006; Ragni 2006; Rumste 2006; Steures 2006a). Because maternal and neonatal morbidity and mortality rates are significantly increased in multiple pregnancies (Fauser 2005; Ombelet 2005), caregivers should take extra care to keep the multiple pregnancy rate to a minimum. Couples should be well informed by their physicians, especially as many couples desire to conceive twins (Ryan 2004) and prefer a higher pregnancy chance over safety.

Some authors state that treatment with OH results in an unacceptable high incidence of high order multiple pregnancies (Gleicher 2000; Nan 1994) and treatment with IUI in natural cycles should be preferred (Fauser 2005; Goverde 2005). Others say that the risk of a multiple pregnancy could be reduced with strict monitoring of the patients (Dickey 2005; Türe 2005); te Velde concluded that IUI with OH is an appropriate treatment option if done with a mild stimulation protocol, careful cycle monitoring and with strict cancellation criteria (te Velde 1999). It is, however, still not known to what extent multiple pregnancies can be avoided if these criteria are met. Besides, the use of strict cycle cancellation criteria might result in a reduced overall pregnancy rate. Several trials using mild stimulation protocols for IUI have been published, showing promising results of acceptable pregnancy rates with very low multiple pregnancy rates (Balasch 2004). As IVF allows better control over reducing the risk of a multiple pregnancy (Gleicher 2000), and IVF with single embryo transfer is more and more accepted, it could be argued that IVF will become a safer treatment option than IUI with OH. However, Goverde et al found IUI to be a more cost-effective treatment than IVF for couples with unexplained or male subfertility (Goverde 2000).

The four studies in our analysis comparing IUI versus IUI with OH all reported multiple pregnancy rates, but only two reported the rates for those with unexplained subfertility. A valid analysis could not be performed. All studies using gonadotropins as the stimulation method reported cancellation criteria. However, the highest multiple pregnancy rate was reported by Goverde 2000 (29% in the OH group compared to 4% in the natural cycle group) despite the use of strict cancellation criteria. It should be noted that 95% of the participants included in this comparison received gonadotropin treatment, which could result in higher multiple pregnancy rates compared to CC treatment (Ombelet 2005).
On the contrary, meta-analyses showed higher pregnancy rates in couples treated with gonadotropins as compared to CC treatment (OR 1.8, 95% CI 1.2 to 2.7) without a significant increase in multiple pregnancies (4% for gonadotropin treatment versus 2% for CC) (Cantineau 2009). It should be noted though that data on multiple pregnancies could only be obtained from three of the seven studies included in the meta-analysis.

Overall completeness and applicability of evidence

To adequately address the question whether IUI with or without OH is an effective treatment for couples with unexplained subfertility, our aim was to analyse the following five treatment comparisons: 1. IUI versus TI, both in a natural cycle; 2. IUI versus TI, both in a stimulated cycle; 3. IUI in a natural cycle versus IUI in a stimulated cycle; 4. IUI in a stimulated cycle versus TI in a natural cycle; and 5. IUI in a natural cycle versus TI in a stimulated cycle. Unfortunately, we were able to perform a meta-analysis for two of these comparisons only, because of the lack of comparable RCTs available for the other comparisons. Therefore, we were not able to answer all questions posed.

Furthermore, we were not able to assess all desired outcomes for each comparison. There were not enough data available to retrieve adequate live birth rates, and there were even less data available for the adverse effects of each treatment modality. Important prognostic factors such as age, duration of subfertility and previous treatment were poorly reported, making it impossible to perform subgroup analyses.

Quality of the evidence

The overall quality of the included trials was suboptimal. This was mainly because of the poorly reported randomisation and allocation methods.

The quality of fertility trials has been criticized repeatedly. One of the areas of particular concern is what statisticians refer to as the ‘unit of analysis’ error (Vail 2003). It is methodologically incorrect to report data per cycle when it is women or couples who are randomised because many of the women will have undergone more than one treatment cycle (Dias 2008; Johnson 2003; Vail 2003). Yet pregnancy rate per cycle is a commonly reported outcome in fertility trials and reviews.

Another methodological difficulty in fertility trials is the use of studies with a crossover design. There have been many discussions about whether a crossover design is appropriate for fertility trials, mainly because patients drop out after treatment success, which results in a selected patient population post-crossover. For this reason, it is said that the crossover design has no place in infertility trials (Daya 1993). A crossover design could result in an over-estimation of the treatment effect (Khan 1996; Norman 2000). Whether this overestimation could be statistically corrected for or whether it is clinically relevant remains under debate (Cohlen 1998; McDonnell 2004; Vail 2003). In this systematic review we focused on live birth rates or pregnancy rates per couple. The couple being the denominator, post-crossover data could not be included because then couples would have received both treatment modalities and results per couple could not be extracted.

The more recent studies adopted expectant management as a control treatment for IUI instead of timed intercourse (Bhattacharya 2008; Steures 2006). Because timing of intercourse (TI) interferes with the natural coital habits of a couple, expectant management has been proposed as the more appropriate comparison treatment for IUI (Wilcox 1995). A recent meta-analysis however shows no significant difference in pregnancy rate between studies comparing IUI versus TI and studies with IUI versus expectant management (Snick 2008). Whether it is appropriate to pool studies including TI and expectant management in a meta-analysis remains unclear.

The data of Bhattacharya 2008 and Steures 2006 were not, however, pooled with data of trials applying TI because these trials comprised comparisons that were not subject to many other trials. It is generally agreed that the aim of fertility treatment should be to achieve a live birth instead of inducing a pregnancy (Land 2003). Healy and others go even further by suggesting that the ‘birth emphasizing a successful singleton at term’ (BESST) outcome should be the standard measure of success for fertility trials (Daya 2003; Fauser 2005; Healy 2004; Min 2004). We have tried to focus on live birth as the main outcome of interest in this analysis. Unfortunately, live birth was reported by only seven of the 12 included studies. We have decided to use live birth data whenever possible for the analyses. If there were not enough live birth data available we used the more often reported pregnancy rates for the main analyses.

Potential biases in the review process

To prevent selection bias, the included studies were independently selected and data extracted by two authors (Cohlen, Verhulst; Hughes and Verhulst respectively). Disagreements were resolved by discussion, keeping the protocol as our guideline to reduce bias. A statistician (Vail) was consulted for the data extraction of complicated crossover trials. We have extracted and calculated the events per randomised couple for this meta-analysis, which resulted in the exclusion of six studies reporting only post-crossover or per cycle data. As a consequence, the analysis is statistically less biased although a selection bias may have occurred.

A funnel plot was done only for the comparison with the most studies (IUI versus TI both in a stimulated cycle) (Figure 3). The funnel plot is reasonably symmetrical, suggesting that a publication bias is unlikely.
It should be noted that Asian countries are underrepresented in the included trials. It is not known whether Asian IUI trials have not been done or could not be found with our search.

**Agreements and disagreements with other studies or reviews**

Previous review articles and meta-analyses by, for example, Aboulghar 2003, Balasch 2004, Cohlen 2005, Costello 2004, Hughes 1997 and Zeyneloglu 1998 have all assessed the effectiveness of IUI and ovarian hyperstimulation. They have, however, all calculated pregnancy rates per cycle, which makes it difficult to compare with our per couple data. Per cycle data produce biased results that may exaggerate treatment results (Dias 2008). This could explain why the pregnancy rates found in our meta-analysis are lower than those generally reported by the above-mentioned authors.

**Authors’ Conclusions**

**Implications for practice**

This systematic review shows evidence that the addition of ovarian hyperstimulation (OH) to intrauterine insemination (IUI) treatment improves live birth rates in couples with unexplained subfertility. A smaller but statistically significant rise in pregnancy rate was found for IUI when compared with time intercourse (TI) in stimulated cycles.

The results of this analysis should be interpreted with caution for daily practice as we could not adequately assess the multiple pregnancy rates and other adverse effects.

Despite the limitations of this review, it shows evidence that IUI with OH is more effective than no treatment at all and could be considered an effective treatment for couples with unexplained subfertility. In couples with a moderate to good prognosis of spontaneously conceiving, abstaining from treatment for several months should be considered. The multiple pregnancy rates should be kept to a minimum by using mild stimulation protocols and strict cancellation criteria. Couples should be fully informed about the risks of IUI and OH and alternative treatment options should also be offered.

**Implications for research**

There is a need to investigate whether the multiple pregnancy risk can be reduced to acceptable levels while still keeping acceptable live birth rates. Therefore a large randomised controlled trial is
needed comparing IUI in natural cycles with low dose stimulated IUI.

Future trials are encouraged to report detailed live birth data (singleton, term) and adverse events such as multiple pregnancies, miscarriage, ectopic pregnancies and ovarian hyperstimulation syndrome.

ACKNOWLEDGEMENTS

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Bhattacharya 2008 [published data only]

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Crosignani 1991 [published data only]

Crosignani 1991b [published data only]

Crosignani 1991c [published data only]

Crosignani 1991d [published data only]

Deaton 1990 [published data only]

Goverde 2000 [published data only]

Guzick 1999 [published data only]

Janko 1998 [published data only]

Karlstrom 1993 [published data only]
References to studies excluded from this review

Aboulghar 1993  (published data only)

Doyle 1991  (published data only)

Evans 1991  (published data only)

Gregoriou 1995  (published data only)

Ho 1998  (published data only)

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Daya 2003


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Cohlen 2005


Costello 2004


Daya 1993


Daya 2003

Intra-uterine insemination for unexplained subfertility (Review)

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Kerin 1984

Khan 1996

Land 2003

McDonnell 2004

Min 2004

Nan 1994

NICE 2004

Norman 2000

Ombleet 2005

Ragni 2006

RCOG 1998

Ripps 1994
Ripps BA, Minhas BS, Carson SA, Buster JE. Intrauterine insemination in fertile women delivers larger numbers of sperm to the peritoneal fluid than intracervical insemination. *Fertility and Sterility* 1994;61(2):398–400.

Rumste 2006

Ryan 2004

Snick 2008

Steures 2006a

Stewart 2003

te Velde 1999

Tur 2005

Vail 2003

Wilcox 1995
Zeyneloglu 1998
*Indicates the major publication for the study
Characteristics of included studies  [ordered by study ID]

Agarwal 2004

| Methods | Trial design: parallel  
|         | Single centre  
|         | Randomisation: random number table  
|         | Allocation concealment: sealed opaque envelopes  
|         | Nr of Pt randomised: IUI+OH 70; TI+OH 70  
|         | Nr of withdrawals: IUI+OH 26 (37%); TI+OH 1 (total 19%)  

| Participants | Couples with unexplained subfertility  
|             | Age: IUI+OH 29.52 (±3.65); TI+OH 28.83 (±4.76)  
|             | Duration of subfertility: IUI+OH 4.91 (±2.72); TI+OH 4.93 (±3.27)  
|             | Basic fertility work up normal, semen normal according to WHO 1987  
|             | Previous treatment: no  

| Interventions | Comparison: IUI+OH versus TI+OH  
|               | Stimulation method: 50-150 mg CC/day, day 3-7  
|               | Ovulation: 10000 IU hCG when not more than 4 follicles of >16mm were present  
|               | Timing of IUI and TI: 36-40hr after HCG  
|               | Duration of treatment: 6 cycles max  

| Outcomes | Live birth and PR per couple and per cycle  
|          | Miscarriage rate  
|          | Ectopic PR  
|          | Multiple pregnancies  
|          | Pregnancy confirmed by USS showing gestational sac  

| Notes | ITT-analysis: possible  
|       | Author provided additional information  
|       | Unbalanced groups: dropouts 37% in IUI group, 1% in TI group  

Risk of bias

| Bias | Authors' judgement | Support for judgement  
|------|--------------------|-----------------------|  
| Random sequence generation (selection bias) | Low risk | Random number table  
| Allocation concealment (selection bias) | Low risk | A - Adequate; sealed opaque envelopes  
| Blinding (performance bias and detection bias) All outcomes | High risk | Blinding was not possible because of the nature of the interventions  

Intra-uterine insemination for unexplained subfertility (Review)
Agarwal 2004  (Continued)

<table>
<thead>
<tr>
<th>Bias</th>
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<th>Support for judgement</th>
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<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>High risk</td>
<td>There was an unequal dropout in the treatment group due to financial reasons</td>
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<td>All outcomes</td>
<td></td>
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</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>Reported on live birth, however authors provided additional information on ongoing pregnancies and twin pregnancies resulting in different data used for meta-analysis</td>
</tr>
<tr>
<td>Other bias</td>
<td>High risk</td>
<td>The financial constraints causing unbalanced groups could also have influenced patient selection, follow-up and treatment compliance</td>
</tr>
</tbody>
</table>

Arcaini 1996

**Methods**
- Trial design: parallel
- Single centre
- Randomisation: method unclear
- Allocation concealment: unclear
- Nr of Pt randomised: IUI+OH 36; TI+OH 32
- Nr of withdrawals: 14 (20.6%)

**Participants**
- Couples with unexplained subfertility
- Age: IUI+OH 34.6 (±4.9); TI+OH 33.4 (±4.7)
- Duration of subfertility: IUI+OH 4.2 (±1.6); TI+OH 3.9 (±2.3)
- Basic fertility work up normal, semen normal, not further specified
- Previous treatment: not stated

**Interventions**
- Comparison: IUI+OH versus TI+OH
- Stimulation method: 100mg CC/day, day 3-7 and 1-3 ampoule hMG/day
- Ovulation: 10000 IU hCG when 2-6 follicles of >17mm were present
- Timing IUI or TI: 24hr and 48 hr after hCG
- Duration of treatment: 5 cycles max

**Outcomes**
- PR per couple
- Miscarriage rate
- Ectopic PR
- Multiple pregnancies
- OHSS
- Pregnancy confirmed by USS

**Notes**
- ITT-analysis: yes
Random sequence generation (selection bias) | Unclear risk | Not stated
---|---|---
Allocation concealment (selection bias) | Unclear risk | B - Unclear
Blinding (performance bias and detection bias) | High risk | Blinding was not possible because of the nature of the interventions
Incomplete outcome data (attrition bias) | Low risk | A total of 16 cancelled treatment cycles is described and analysed according to intention to treat. Patients who dropped out are clearly stated in a table
Selective reporting (reporting bias) | Unclear risk | Did not report on live birth, however, did not intend to report on live birth

**Arici 1994**

**Methods**
- Trial design: crossover (after 1 cycle)
- Single centre
- Randomisation: computer generated random number table
- Allocation concealment: computer system utilising locked files
- Nr of Pt randomised: 26
- Nr of withdrawals: not clear

**Participants**
- Couples with unexplained subfertility and couples with male factor subfertility
- Age: mean 33 yrs (range 24-41)
- Duration of subfertility: mean 3.5 yrs (range 1-15 yr)
- Unexplained subfertility: basic fertility work up normal, semen normal according to WHO 1987 criteria
- Previous treatment: no

**Interventions**
- Comparison: IUI+NC versus IUI+OH
- Stimulation method: 50 mg CC/day, day 5-9
- Timing:
  - Natural cycle: urinary LH test, IUI on day of LH peak and the next day
  - Stimulated cycle: 10000 IU hCG when at least 1 follicle of 18mm was present; IUI 32 hr after hCG
- No cancellation criteria were given
- Duration of treatment: 4 cycles max

**Outcomes**
- Live birth and PR per couple
- PR per 1st cycle
- PR per cycle
- Miscarriage rate
- Ectopic PR
- Multiple pregnancies
### Arici 1994 (Continued)

| Notes | Pregnancy confirmed by USS showing gestational sac  
| ITT analysis: yes  
| Author provided additional information  
| 5 Pt with treated minimal endometriosis were included as unexplained subfertility |

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Computer generated random number table</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>A - Adequate; computer system utilizing locked files</td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias) All outcomes</td>
<td>High risk</td>
<td>Blinding was not possible because of the nature of the interventions</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Low risk</td>
<td>Author gave additional information on dropout rates of the couples with unexplained subfertility. Of the 26 women with unexplained subfertility, dropout occurred after 1 treatment cycle. Post-crossover data are not included in the meta-analysis</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>Live birth data were obtained from the author</td>
</tr>
</tbody>
</table>

### Bhattacharya 2008

| Methods | Trial design: parallel  
| Multi centre (four teaching hospitals, one general hospital Scotland)  
| Randomisation: computer generated randomisation schedule  
| Allocation concealment: central telephone system  
| Nr of Pt randomised: 509 with unexplained subfertility only (total 580).  
| Nr of withdrawals: 4 |
| Participants | Couples with unexplained subfertility, (mild male factor infertility and minimal endometriosis)  
| Age: TI+NC 32 (±3.4); TI+OH 32 (±3.5); IUI+NC 32 (±3.7)  
| Duration of subfertility: minimal 2 years, median 30 months all groups  
| Basic fertility work up normal, semen normal according to WHO (sperm motility<20% included)  
| Previous treatment: not stated |
### Interventions

Comparison: TI (expectant management) +NC versus TI+OH versus IUI+NC  
Stimulation method: 50 mg CC/day (starting dose), day 2-6  
Ovulation: confirmed by progesterone measure in TI+OH group, and urinary LH surge in IUI+NC group  
Timing of IUI and TI: IUI 20-30hr after LH surge, Timing intercourse advised on cycle day 12-18  
Duration of treatment: 6 cycles max

### Outcomes

Live birth and PR per couple  
Miscarriage rate  
Ectopic PR  
Multiple pregnancies  
Pregnancy confirmed by USS showing gestational sac and fetal heart beat

### Notes

The author provided additional data on the couples with unexplained subfertility only  
The baseline characteristics of the patients reported are from the group total. ITT analysis was therefore possible and performed  
Author provided additional information.

### Risk of bias

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<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Sequence generated by independent statistican</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>A - Adequate; central telephone randomisation system</td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias)</td>
<td>High risk</td>
<td>Blinding was not possible because of the nature of the interventions</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>Loss to follow-up and patients who received alternative treatment are presented in a flow-chart</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>Live birth data and adverse events are published</td>
</tr>
</tbody>
</table>
### Methods
Trial design: parallel  
Single centre  
Randomisation: blocked randomisation scheme  
Allocation concealment: numbered sealed envelopes  
Nr of Pt randomised: 100  
Total dropouts: 12 (12%)

### Participants
Couples with unexplained subfertility  
Age: IUI+OH 31.8 (±3.1); TI+OH 32.1 (±4.0)  
Duration of subfertility: IUI +OH 4.7 (±2.0); TI+OH 5.3 (±2.6)  
Basic fertility work up normal and semen 15 million motile per ejaculate  
Previous treatment: not stated

### Interventions
Comparison: IUI+OH versus TI+OH  
Stimulation method: FSH 150 IU/day and GnRH nasal spray from day 21 on  
Ovulation: 5000IU hCG when <4 follicles >16mm  
hCG post ovulatory for luteal support  
Timing TI: 24 + 48 hr after hCG  
Timing IUI: 36-48 hr after hCG  
Duration of treatment: 3 cycles max

### Outcomes
PR per couple and per cycle  
Total delivered  
Multiple pregnancies  
Ectopic  
Miscarriage rate

### Notes
ITT-analysis: possible  
IUI was not possible on Sundays

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
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<tbody>
<tr>
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<td>Low risk</td>
<td>Blocked randomisation scheme</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>A - Adequate; numbered sealed envelopes</td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias)</td>
<td>High risk</td>
<td>Blinding was not possible because of the nature of the interventions</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Unclear risk</td>
<td>8/50 withdrawn and 6 treatment cycles cancelled in TI group, 4/50 withdrawn and 11 treatment cycles cancelled in IUI group. Reason for cycle cancellation was excessive response. Reason for withdrawal was not stated</td>
</tr>
</tbody>
</table>
**Chung 1995**  (Continued)

<table>
<thead>
<tr>
<th>Selective reporting (reporting bias)</th>
<th>Low risk</th>
<th>Live birth data and complication numbers were reported.</th>
</tr>
</thead>
</table>

**Crosignani 1991**

**Methods**

- Data from centre 10: Hedon, Montpellier, France
- Trial design: cross over (after 1 cycle)
- Multi centre (19 European fertility centres, 4 centres comparing IUI versus TI)
- Randomisation: not clear
- Allocation concealment: unclear
- Nr of Pt randomised: unclear
- Nr of Pt analysed: total 90 (centre 10; 18 patients)
- Nr of withdrawals: unclear

**Participants**

- Couples with unexplained subfertility
- Age: <38yrs
- Duration of subfertility: >3yrs
- Basic fertility work up normal, semen normal according to WHO 1987
- Previous treatment: not stated

**Interventions**

- Comparison: IUI+OH versus TI+OH
- Stimulation method: not stated
- Ovulation: not described
- Timing: not described
- No cancellation criteria were given
- Duration of treatment: 2 cycles max

**Outcomes**

- PR per 1st cycle
- PR per cycle

**Notes**

- ITT-analysis: not possible
- Author replied; could not provide additional information
- Multicentre ESHRE trial.
- Only 4 infertility centres compared IUI with superovulation alone. These centres were included in the analysis

**Risk of bias**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Each centre used own randomisation method. The per centre method could not be obtained</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>B - Unclear; each centre used own treatment allocation method. The per centre method could not be obtained</td>
</tr>
</tbody>
</table>
### Crosignani 1991

**Continued**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blinding (performance bias and detection bias) All outcomes</td>
<td>High risk</td>
<td>Blinding was not possible because of the nature of the interventions</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>High risk</td>
<td>Details on patient withdrawal or loss to follow-up were not stated</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>Live birth data were not reported</td>
</tr>
</tbody>
</table>

### Crosignani 1991b

- **Methods**
  - Data from centre 13: Willemsen, Nijmegen, the Netherlands
  - Nr of Pt analysed: 7

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blinding (performance bias and detection bias) All outcomes</td>
<td>High risk</td>
<td></td>
</tr>
</tbody>
</table>

### Crosignani 1991c

- **Methods**
  - Data from centre 16: Pellicer, Valencia, Italy
  - Nr of Pt analysed: 35

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
</table>
### Crosignani 1991c (Continued)

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blinding (performance bias and detection bias) All outcomes</td>
<td>High risk</td>
<td></td>
</tr>
</tbody>
</table>

### Crosignani 1991d

<table>
<thead>
<tr>
<th>Methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data from centre 19: Martinez, Amsterdam, the Netherlands</td>
</tr>
<tr>
<td>Nr of Pt analysed: 30</td>
</tr>
</tbody>
</table>

#### Participants

- **Interventions**
  - **Stimulation method:** 50 mg CC/day, day 5-9
  - **Timing:**
    - Natural cycle: urinary LH and BBT timed intercourse
    - Stimulated cycle: 10000 IU hCG when lead follicle was estimated to be at least 18mm.
    - IUI 36hr after hCG injection.
  - No cancellation criteria were given

<table>
<thead>
<tr>
<th>Deaton 1990</th>
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</thead>
</table>

<table>
<thead>
<tr>
<th>Methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial design: crossover (after 4 cycles)</td>
</tr>
<tr>
<td>Single centre</td>
</tr>
<tr>
<td>Randomisation: unclear</td>
</tr>
<tr>
<td>Allocation concealment: unclear</td>
</tr>
<tr>
<td>Nr of Pt randomised: 67</td>
</tr>
<tr>
<td>Nr of Pt analysed: 51 total, unexplained: 24</td>
</tr>
<tr>
<td>Nr of withdrawals: 4 pre-crossover (6%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Couples with unexplained subfertility and couples with surgically treated endometriosis</td>
</tr>
<tr>
<td>Age: 33 (±4.0)</td>
</tr>
<tr>
<td>Duration of subfertility: 3.5 (±1.7)</td>
</tr>
<tr>
<td>Basic fertility work up normal, semen normal according to WHO criteria 1987</td>
</tr>
<tr>
<td>Previous treatment: not stated</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comparison: IUI+OH versus TI+NC</td>
</tr>
<tr>
<td>Stimulation method: 50 mg CC/day, day 5-9</td>
</tr>
<tr>
<td>Timing:</td>
</tr>
<tr>
<td>Natural cycle: urinary LH and BBT timed intercourse</td>
</tr>
<tr>
<td>Stimulated cycle: 10000 IU hCG when lead follicle was estimated to be at least 18mm.</td>
</tr>
<tr>
<td>IUI 36hr after hCG injection.</td>
</tr>
<tr>
<td>No cancellation criteria were given</td>
</tr>
</tbody>
</table>
### Deaton 1990 (Continued)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Duration of treatment: 8 cycles max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing pregnancy rate</td>
<td></td>
</tr>
<tr>
<td>Multiple pregnancies</td>
<td></td>
</tr>
<tr>
<td>Ectopic pregnancies</td>
<td></td>
</tr>
<tr>
<td>Miscarriage rate</td>
<td></td>
</tr>
<tr>
<td>OHSS</td>
<td></td>
</tr>
<tr>
<td>Pregnancy: not further defined</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Notes</th>
<th>ITT-analysis: not possible</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients with unexplained subfertility and endometriosis were included in this study; three patients with moderate and no patients with severe endometriosis</td>
</tr>
</tbody>
</table>

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Sequence generation not stated</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>B - Unclear</td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias) All outcomes</td>
<td>High risk</td>
<td>Blinding was not possible because of the nature of the interventions</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Low risk</td>
<td>16/67 patients excluded from analysis due to anovulation, poor semen quality or inability to follow the treatment protocol. Of the remaining 51 patients, 6 couples did not complete treatment because of illness or relocation. 4/51 dropped out before crossover</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>Live birth rate was not reported.</td>
</tr>
</tbody>
</table>

### Goverde 2000

<table>
<thead>
<tr>
<th>Methods</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial design: parallel</td>
<td></td>
</tr>
<tr>
<td>Single centre</td>
<td></td>
</tr>
<tr>
<td>Randomisation: computer generated randomisation schedule</td>
<td></td>
</tr>
<tr>
<td>Allocation concealment: numbered, masked and sealed envelopes</td>
<td></td>
</tr>
<tr>
<td>A power calculation was performed</td>
<td></td>
</tr>
<tr>
<td>Nr of patients randomised: 120 (unexplained IUI+NC and IUI+TI), 258 total</td>
<td></td>
</tr>
<tr>
<td>Nr of withdrawals: unclear</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Participants</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Couples with unexplained subfertility and couples with male factor subfertility</td>
<td></td>
</tr>
<tr>
<td>Age: IUI+NC 31.6 (±3.7); IUI+OH 31.7 (±3.9)</td>
<td></td>
</tr>
<tr>
<td>Duration of subfertility: IUI+NC 3.9 (±1.7); IUI+OH 4.2 (±1.9)</td>
<td></td>
</tr>
</tbody>
</table>
Basic fertility work up normal, semen normal when >20 million progressive motile in ejaculate
Previous treatment: not stated

Interventions
Comparison: IUI+NC versus IUI+OH (versus IVF)
Stimulation method: 75 IU FSH (starting dose) until 1-3 follicles of 18mm were seen on USS
hCG was withheld if >3 follicles of 18mm or > 6 of 14 mm were present
Timing:
Stimulated cycle: 10000 IU hCG, IUI 40-42 hr after hCG;
Natural cycle: IUI 20-30 hr after detection of urinary LH-surge.
Cycles were cancelled when >3 follicles of 18mm or >6 follicles of 14 mm were present
Duration of treatment: 6 cycles max

Outcomes
Live birth per couple
OHSS

Notes
ITT-analysis: yes
Some dropouts because of spontaneous pregnancy

Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Computer generated randomisation schedule</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>A - Adequate; numbered, masked and sealed envelopes</td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias)</td>
<td>High risk</td>
<td>Blinding was not possible because of the nature of the interventions</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Unclear risk</td>
<td>7/120 withdrew before 1st treatment cycle. Details on dropout not separately available for unexplained subfertility. Some patients dropped out because of spontaneous pregnancy. It is not known whether these patients are included in the IUI unexplained subfertility group</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>Live birth and complication data were reported</td>
</tr>
</tbody>
</table>
### Guzick 1999

#### Methods
- **Trial design:** Parallel
- **Multi centre (10 clinical sites)**
- **Randomisation:** computer generated permuted block
- **Allocation concealment:** locked computer files
- **Nr of Pt randomised:** 932 (465 treated with IUI)
- **Nr of Pt with unexplained subfertility:** 211
- **Nr of withdrawals:** 72 total (15%)

#### Participants
- Couples with unexplained subfertility and couples with stage I or II treated endometriosis or male factor subfertility
- **Age:** IUI+NC 32 (±4)
- **IUI+OH 32 (±4)**
- **Duration of subfertility:** IUI+NC 3.8 (±2.6); IUI+OH 3.5 (±2.2)
- **Basic fertility work up normal, semen normal (according to WHO 1992)**
- **Previous treatment:** No previous treatment. (Pt excluded if previous ART)

#### Interventions
- **Comparison:** IUI+NC versus IUI+OH
- **Stimulation method:** 150 IU FSH/day, day 3-7
- **Ovulation:** IUI+OH: 10000 IU hCG when 2 follicles of > 18mm were present
- **IUI+NC:** urine LH testing
- **Timing:** IUI+OH: 36-40 hr after hCG
- **IUI+NC:** IUI the day after urinary LH surge
- **Cycles were cancelled if serum E2 concentration >300pg/ml**
- **Duration of treatment:** 4 cycles max

#### Outcomes
- **Live birth per couple**
- **PR per couple**
- **Miscarriage rate**
- **Ectopic PR**
- **Multiple pregnancies**
- **OHSS**
- **Pregnancy defined by two positive HCG tests. Confirmed by live birth**

#### Notes
- **ITT-analysis:** not possible
- **Author replied; provided additional information**

### Risk of bias

<table>
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</table>

---

*Intra-uterine insemination for unexplained subfertility (Review)*

Copyright © 2011 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
Incomplete outcome data (attrition bias)  
All outcomes  
Unclear risk  
Withdrawal rates of the total group were presented: 4/465 treatment related withdrawal, 27/465 not treatment related. Numbers for unexplained subfertility group are not known

Selective reporting (reporting bias)  
Low risk  
Live birth and complication data were reported

### Janko 1998

**Methods**
- Trial design: parallel
- Single centre
- Randomisation: not clear
- Allocation concealment: unclear
- Nr of Pt randomised: 72
- Nr of withdrawals: not stated

**Participants**
- Couples with unexplained subfertility
- Age: not stated
- Duration of subfertility: >3 yrs
- Basic fertility work up normal, semen normal not further specified
- Previous treatment: not stated

**Interventions**
- Comparison: IUI+OH versus TI+OH
- Stimulation method: hMG (10 amp per cycle)
- Ovulation: 10000 IU hCG
- Timing: not specified
- No cancellation criteria were given.
- Duration of treatment: 3 cycles max

**Outcomes**
- PR per cycle
- Pregnancy not further defined

**Notes**
- ITT-analysis: possible
- Abstract only.
- Data calculated.

### Risk of bias

<table>
<thead>
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<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
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<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Not stated</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>B - Unclear; not stated</td>
</tr>
</tbody>
</table>
### Janko 1998  
(Continued)

<table>
<thead>
<tr>
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<td>High risk</td>
<td>Blinding was not possible because of the nature of the interventions</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>High risk</td>
<td>Not available</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>High risk</td>
<td>In this abstract the reported outcome data are minimal</td>
</tr>
</tbody>
</table>

### Karlstrom 1993

<table>
<thead>
<tr>
<th>Methods</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial design: Parallel</td>
<td></td>
</tr>
<tr>
<td>Single centre</td>
<td></td>
</tr>
<tr>
<td>Randomisation: not clear</td>
<td></td>
</tr>
<tr>
<td>Allocation concealment: unclear</td>
<td></td>
</tr>
<tr>
<td>Nr of Pt randomised: not clear</td>
<td></td>
</tr>
<tr>
<td>Nr of Pt analysed: 79</td>
<td></td>
</tr>
<tr>
<td>Nr of withdrawals: not clear</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Participants</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Couples with unexplained subfertility and minimal or mild endometriosis</td>
<td></td>
</tr>
<tr>
<td>Age: 32 (range 21-38)</td>
<td></td>
</tr>
<tr>
<td>Duration of subfertility: 5 (range 2-14)</td>
<td></td>
</tr>
<tr>
<td>Basic fertility work up normal, semen normal according to WHO 1987.</td>
<td></td>
</tr>
<tr>
<td>Previous treatment: no</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Interventions</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Comparison: IUI+OH versus TI+OH (vs DIPI+OH vs IUI and DIPI+OH)</td>
<td></td>
</tr>
<tr>
<td>Stimulation method 1: 150IU hMG starting dose, till one follicle of at least 17 mm was present or the detection of a LH surge in serum or urine.</td>
<td></td>
</tr>
<tr>
<td>Monitoring: USS and serum E2</td>
<td></td>
</tr>
<tr>
<td>Ovulation: 10000 IU hCG</td>
<td></td>
</tr>
<tr>
<td>Timing: IUI 36-41 hr after hCG or 24 hr after detection of LH surge. TI the two following nights after hCG injection</td>
<td></td>
</tr>
<tr>
<td>Cycles were cancelled according to serum E2 rise.</td>
<td></td>
</tr>
<tr>
<td>Duration of treatment: 1 cycle max</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>PR per cycle</td>
<td></td>
</tr>
<tr>
<td>Ectopic PR</td>
<td></td>
</tr>
<tr>
<td>Pregnancy not further defined</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Notes</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT-analysis: not possible</td>
<td></td>
</tr>
<tr>
<td>When ovulation occurred during the weekend, Pt were transferred to TI group</td>
<td></td>
</tr>
</tbody>
</table>

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Authors’ judgement</td>
<td></td>
</tr>
<tr>
<td>Support for judgement</td>
<td></td>
</tr>
</tbody>
</table>
Random sequence generation (selection bias) | Unclear risk | Not stated
---|---|---
Allocation concealment (selection bias) | Unclear risk | B - Unclear; not stated
Blinding (performance bias and detection bias) | High risk | Blinding was not possible because of the nature of the interventions
Incomplete outcome data (attrition bias) | Low risk | 4 withdrawals in clomiphene group due to absent LH surge, 5 withdrawals in hMG group due to absent LH surge, fast oestrogen rise or personal reasons
Selective reporting (reporting bias) | Unclear risk | Live birth data were not reported

Karlstrom 1993 b

Methods
See Karlstrom 1993a
Group underwent different stimulation method

Participants

Interventions
Stimulation method 2: 100mg CC/day for 5 days
Monitoring + Ovulation; urinary LH timed.
Timing: IUI 20-28 hr after LH surge, TI day of LH surge and day after

Outcomes

Notes

Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blinding (performance bias and detection bias)</td>
<td>High risk</td>
<td></td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Intra-uterine insemination for unexplained subfertility (Review)
Copyright © 2011 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
| Methods | Trial design: parallel  
Randomisation: computer generated random number list  
Allocation concealment: numbered opaque sealed envelopes  
Nr of Pt randomised: 108  
Nr of Pt analysed: 103  
Nr of withdrawals: 5 (4.6%) |
|----------|------------------------------------------------------------|
| Participants | Couples with unexplained and couples with mild male factor subfertility  
Age: 33.1 (±5.2)  
Duration of subfertility: 4.3 (±1.4)  
Basic fertility work up normal, semen normal according to WHO 1987 criteria  
Previous treatment: yes, all couples |
| Interventions | Comparison: IUI+OH versus TI+OH  
Stimulation method: 3 amp FSH/day  
Monitoring: USS and plasma E2  
Ovulation: 10000 IU hCG when at least 2 follicles of 16mm were present  
Timing: TI 12 hr after HCG, IUI 30-36 hr after HCG  
Cycles cancelled when plasma E2 level > 1500pg/ml  
Duration of treatment: 3 cycles max |
| Outcomes | Live birth per couple  
PR/couple  
Miscarriage  
Multiple pregnancies  
OHSS  
Pregnancy confirmed by USS showing fetal heart activity |
| Notes | ITT analysis: possible  
Author provided additional information  
All patients have had previous fertility treatment  
Pt with minor abnormalities were excluded from the study |

**Risk of bias**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Computer generated random number list</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>A - Adequate; numbered opaque sealed envelopes</td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias) All outcomes</td>
<td>High risk</td>
<td>Blinding was not possible because of the nature of the interventions</td>
</tr>
</tbody>
</table>
### Melis 1995 (Continued)

| Incomplete outcome data (attrition bias) | Low risk | Exclusion numbers were published for the overall group. The author provided additional information: 1/52 (IUI+OH group) withdrew, 4/56 (TI+OH group) withdrew. Reasons for dropout were family problems, poor response or exaggerated response. |
| Selective reporting (reporting bias) | Low risk | Live birth data and complication numbers were available for analysis. |

### Murdoch 1991

| Methods | Trial design: parallel  
Randomisation: random number sequence  
Allocation concealment: via sequentially numbered opaque sealed envelopes  
Nr of Pt randomised: 39  
IUI+NC 19; IUI+OH 20  
Nr of withdrawals: 5 (13%) |
| Participants | Couples with unexplained subfertility  
Age: IUI+NC 30.5 (±3.1); IUI+OH 30.1 (±2.9)  
Duration of subfertility: IUI+NC 5.7 (±2.4); IUI+OH 5.1 (±1.9)  
Basic fertility work up done, semen normal (according to WHO 1987)  
Previous treatment: no |
| Interventions | Comparison: IUI+NC versus IUI+OH (vs GIFT)  
Stimulation method: 75 IU hMG/day and 200 micro gram buserelin 4 times daily intranasal  
Ovulation: 5000 IU hCG, when < 4 follicles of >16mm were seen.  
Timing: 30-36 hr after hCG  
Natural cycle: IUI on alternate days until ovulation confirmed on USS  
Cycles were cancelled if >4 dominant follicles were present  
Duration of treatment: 3 cycles max |
| Outcomes | PR per couple and per cycle  
Live birth  
Multiple pregnancies  
Clinical pregnancy defined by USS showing fetal heart activity |
| Notes | ITT analysis: yes  
Author provided additional information  
1 pregnancy between treatment cycles  
10 cycles were abandoned because no treatment available at the weekend |

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
</table>
### Murdoch 1991  (Continued)

<table>
<thead>
<tr>
<th>Random sequence generation (selection bias)</th>
<th>Low risk</th>
<th>Computer generated random number sequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>A - Adequate; numbered opaque sealed envelopes</td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias) All outcomes</td>
<td>High risk</td>
<td>Blinding was not possible because of the nature of the interventions</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Low risk</td>
<td>Drop-out rate 3/19 (IUI+NC), and 2/20 (IUI+OH). Reasons not stated. Data on cycle cancellation are reported</td>
</tr>
</tbody>
</table>

### Steures 2006

**Methods**
- Trial design: parallel
- Multi centre: 26 fertility centres in the Netherlands
- Randomisation: computer generated sequence in balanced blocks
- Allocation concealment: via opaque sealed envelopes
- Nr of Pt randomised: 253
  - IUI+OH 127; TI (expectant management)+NC 126
- Nr of withdrawals: 3 (IUI+OH) and 2 (TI+NC), 2 still pregnant (TI + NC)

**Participants**
- Couples with unexplained subfertility and an intermediate prognosis of conceiving within the next 12 months (Hunault 30-40%)
- Age: IUI+OH 33 (±3.4); TI+NC 33 (±3.19)
- Duration of subfertility: IUI+OH 2.0 (±0.5);TI+NC 1.91 (±0.5)
- Basic fertility work up done, semen analysis according to WHO 1987, normal postcoital test
- Previous treatment: not stated

**Interventions**
- Comparison: IUI+OH versus TI (expectant management)+NC
- Stimulation method: FSH 37-150 IU/day or 50-150 mg CC/day
- Monitoring: USS
- Ovulation: 5000 or 10000 IU hCG
- Timing: IUI 36-40 hr after hCG
- Cycles were cancelled when >3 follicles of 16mm or >5 follicles of 12mm were present
- Duration of treatment: 6 months

**Outcomes**
- Live birth/couple
- PR/couple
- Miscarriage rate
- Multiple pregnancies
Notes

ITT analysis: yes
Author provided additional information.
Only couples with an intermediate prognosis of conceiving were included, this influences the possible treatment effect

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Computer generated sequence in balanced blocks</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>A - Adequate; via opaque sealed envelopes</td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias)</td>
<td>High risk</td>
<td>Blinding was not possible because of the nature of the interventions</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>IU1+OH group 3 patients lost to follow up, TI+NC group 2 lost to follow up 2 still pregnant</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>Live birth and complications reported</td>
</tr>
</tbody>
</table>

CC: clomiphene citrate
DIPI: direct intraperitoneal insemination
FSH: follicle stimulating hormone
hCG: human chorionic gonadotropin
hMG: human menopausal gonadotropin
IUI: intra-uterine insemination
OH: ovarian hyperstimulation
USS: ultrasound scan

Characteristics of excluded studies  [ordered by study ID]

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aboulghar 1993</td>
<td>The trial was not randomised</td>
</tr>
<tr>
<td>Doyle 1991</td>
<td>No pre-crossover data available</td>
</tr>
<tr>
<td>Evans 1991</td>
<td>No pre-crossover data available</td>
</tr>
<tr>
<td>Gregoriou 1995</td>
<td>No pre-crossover data available</td>
</tr>
<tr>
<td>Source</td>
<td>Notes</td>
</tr>
<tr>
<td>-------------</td>
<td>------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Ho 1998</td>
<td>Abstract, full article not available. No separate data for couples with unexplained subfertility</td>
</tr>
<tr>
<td>Kirby 1991</td>
<td>No pre-crossover data available</td>
</tr>
<tr>
<td>Martinez 1990</td>
<td>No per woman data. Biochemical pregnancies only reported</td>
</tr>
<tr>
<td>Martinez 1991</td>
<td>No pre-crossover data available</td>
</tr>
<tr>
<td>Nulsen 1990</td>
<td>The trial (published as full paper in 1993) was not randomised</td>
</tr>
<tr>
<td>Nulsen 1993</td>
<td>The trial (also published as an abstract in 1990) was not randomised</td>
</tr>
<tr>
<td>Prentice 1995</td>
<td>This trial was quasi randomised, on the basis of hospital case record number</td>
</tr>
<tr>
<td>Serhal 1988</td>
<td>The trial was not randomised</td>
</tr>
<tr>
<td>Tummon 1997</td>
<td>The participants in this trial were all diagnosed with endometriosis</td>
</tr>
<tr>
<td>Zikopoulos 1993</td>
<td>No pre-crossover data available</td>
</tr>
</tbody>
</table>
## DATA AND ANALYSES

### Comparison 1. IUI versus TI or expectant management both in natural cycle

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Live birth rate per couple (all cycles)</td>
<td>1</td>
<td></td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>2 Pregnancy rate per couple (all cycles)</td>
<td>1</td>
<td></td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>3 Multiple pregnancy rate per couple</td>
<td>1</td>
<td></td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>4 Miscarriage rate per couple</td>
<td>1</td>
<td></td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>5 Ectopic pregnancy rate per couple</td>
<td>1</td>
<td></td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>Totals not selected</td>
</tr>
</tbody>
</table>

### Comparison 2. IUI versus TI both in stimulated cycle

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Live birth rate per couple (all cycles)</td>
<td>2</td>
<td>208</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>1.59 [0.88, 2.88]</td>
</tr>
<tr>
<td>1.1 Gonadotropins</td>
<td>2</td>
<td>208</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>1.59 [0.88, 2.88]</td>
</tr>
<tr>
<td>2 Pregnancy rate per couple (all cycles)</td>
<td>10</td>
<td>517</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>1.68 [1.13, 2.50]</td>
</tr>
<tr>
<td>2.1 Clomiphene Citrate</td>
<td>1</td>
<td>40</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>0.30 [0.03, 2.93]</td>
</tr>
<tr>
<td>2.2 Gonadotropins</td>
<td>4</td>
<td>319</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>1.68 [1.03, 2.75]</td>
</tr>
<tr>
<td>2.3 Clomiphene Citrate and Gonadotropins</td>
<td>1</td>
<td>68</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>2.62 [0.98, 6.98]</td>
</tr>
<tr>
<td>2.4 Clomiphene citrate OR Gonadotropins</td>
<td>4</td>
<td>90</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>1.62 [0.52, 5.05]</td>
</tr>
<tr>
<td>3 Ovarian Hyperstimulation Syndrome rate per women</td>
<td>2</td>
<td></td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>3.1 Gonadotropins</td>
<td>1</td>
<td>108</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>0.0 [0.0, 0.0]</td>
</tr>
<tr>
<td>3.2 Clomiphene Citrate and Gonadotropins</td>
<td>1</td>
<td>68</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>2.75 [0.11, 69.83]</td>
</tr>
<tr>
<td>4 Multiple pregnancy rate per couple</td>
<td>4</td>
<td>316</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>1.46 [0.55, 3.87]</td>
</tr>
<tr>
<td>4.1 Clomiphene Citrate</td>
<td>1</td>
<td>40</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>0.43 [0.02, 11.18]</td>
</tr>
<tr>
<td>4.2 Gonadotropins</td>
<td>2</td>
<td>208</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>1.61 [0.44, 5.89]</td>
</tr>
<tr>
<td>4.3 Clomiphene Citrate and Gonadotropins</td>
<td>1</td>
<td>68</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>1.88 [0.32, 11.00]</td>
</tr>
<tr>
<td>5 Miscarriage rate per couple</td>
<td>2</td>
<td>208</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>1.66 [0.56, 4.88]</td>
</tr>
<tr>
<td>5.1 Gonadotropins</td>
<td>2</td>
<td>208</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>1.66 [0.56, 4.88]</td>
</tr>
</tbody>
</table>
### Comparison 3. IUI in natural cycle versus IUI in stimulated cycle

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1 Live birth rate per couple (all cycles)</strong></td>
<td>4</td>
<td>396</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>2.07 [1.22, 3.50]</td>
</tr>
<tr>
<td>1.1 Clomiphene Citrate</td>
<td>1</td>
<td>26</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>3.75 [0.29, 47.99]</td>
</tr>
<tr>
<td>1.2 Gonadotropins</td>
<td>3</td>
<td>370</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>2.02 [1.18, 3.45]</td>
</tr>
<tr>
<td><strong>2 Pregnancy rate per couple (all cycles)</strong></td>
<td>4</td>
<td>396</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>2.14 [1.26, 3.61]</td>
</tr>
<tr>
<td>2.1 Clomiphene Citrate</td>
<td>1</td>
<td>26</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>6.43 [0.56, 73.35]</td>
</tr>
<tr>
<td>2.2 Gonadotropins</td>
<td>3</td>
<td>370</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>2.02 [1.18, 3.45]</td>
</tr>
<tr>
<td><strong>3 Ovarian Hyperstimulation Syndrome rate per women</strong></td>
<td>3</td>
<td></td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>3.1 Clomiphene Citrate</td>
<td>1</td>
<td>26</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>0.0 [0.0, 0.0]</td>
</tr>
<tr>
<td>3.2 Gonadotropins</td>
<td>2</td>
<td>159</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>0.0 [0.0, 0.0]</td>
</tr>
<tr>
<td><strong>4 Multiple pregnancy rate per couple</strong></td>
<td>2</td>
<td></td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>4.1 Clomiphene Citrate</td>
<td>1</td>
<td>26</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>0.0 [0.0, 0.0]</td>
</tr>
<tr>
<td>4.2 Gonadotropins</td>
<td>1</td>
<td>39</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>3.0 [0.11, 78.27]</td>
</tr>
<tr>
<td><strong>5 Miscarriage rate per couple</strong></td>
<td>1</td>
<td></td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>5.1 Clomiphene Citrate</td>
<td>1</td>
<td></td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>0.0 [0.0, 0.0]</td>
</tr>
<tr>
<td>5.2 Gonadotropins</td>
<td>0</td>
<td></td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>0.0 [0.0, 0.0]</td>
</tr>
<tr>
<td><strong>6 Ectopic pregnancy rate per couple</strong></td>
<td>3</td>
<td></td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>6.1 Clomiphene Citrate</td>
<td>1</td>
<td>26</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>0.0 [0.0, 0.0]</td>
</tr>
<tr>
<td>6.2 Gonadotropins</td>
<td>2</td>
<td>250</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>6.48 [0.33, 127.09]</td>
</tr>
</tbody>
</table>

### Comparison 4. IUI in stimulated cycle versus TI or expectant management in natural cycle

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1 Live birth rate per couple (all cycles)</strong></td>
<td>1</td>
<td></td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td><strong>2 Pregnancy rate per couple (all cycles)</strong></td>
<td>2</td>
<td></td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>2.1 Clomiphene Citrate</td>
<td>1</td>
<td>51</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>3.2 [0.82, 12.50]</td>
</tr>
<tr>
<td>2.2 Clomiphene Citrate or Gonadotropins</td>
<td>1</td>
<td>253</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>0.80 [0.45, 1.42]</td>
</tr>
<tr>
<td><strong>3 Ovarian Hyperstimulation Syndrome rate per women</strong></td>
<td>1</td>
<td></td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>Totals not selected</td>
</tr>
</tbody>
</table>